

Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 088 551 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:

04.04.2001 Bulletin 2001/14

(51) Int. Cl.⁷: **A61K 31/18**

(21) Application number: **99926769.3**

(86) International application number:

PCT/JP99/03343

(22) Date of filing: **23.06.1999**

(87) International publication number:

WO 00/00187 (06.01.2000 Gazette 2000/01)

(84) Designated Contracting States:

**AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL
PT SE**

(72) Inventor:

**YOSHINAGA, Kouji
Yamanouchi Pharmaceut. Co., Ltd.
Tokyo 174-8612 (JP)**

(30) Priority: **26.06.1998 JP 17949798**

(71) Applicant:

**YAMANOUCHI PHARMACEUTICAL CO. LTD.
Tokyo 103-8411 (JP)**

(74) Representative:

**Geering, Keith Edwin
REDDIE & GROSE
16 Theobalds Road
London WC1X 8PL (GB)**

(54) **MEDICINAL COMPOSITIONS FOR TREATING EVACUATORY INSUFFICIENCY**

(57) A therapeutic agent for voiding dysfunction associated with neurogenic bladder where said agent contains tamsulosin or a pharmaceutically acceptable salt thereof.

EP 1 088 551 A1

Description

Technical Field

- 5 [0001] The present invention relates to a pharmaceutical agent and, more particularly, it relates to a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

Background Art

- 10 [0002] Bladder and urethra which are called lower urinary tracts participate in a voiding function and the function is governed by the three types of nerves - sympathetic nerves, parasympathetic nerve and somatic nerve (pudendal nerve). Sympathetic nerve participates in accumulation of urine while parasympathetic nerve participates in urination and pudendal nerve is always active during accumulation of urine showing an action of closing the external urethra sphincter muscle (cf. *Rinsho to Kenkyu*, 71(5):1180, 1994).
- 15 [0003] There are various diseases which cause the urinary dysfunction and main ones are classified into (1) neurogenic bladder caused by cerebrospinal disease, cerebrovascular accident, diabetes mellitus, peripheral nervous disturbance, etc., (2) organic lower urinary tract obstruction such as benign prostatic hyperplasia and urethral stricture and (3) contraction insufficiency of bladder caused by stress urinary incontinence in adult females, prostatitis, prostatic cancer and anticholinergic agents as well as others which are called LUTS and there are various mechanisms for onset of
- 20 urinary dysfunction depending upon the diseases for the cause (cf. *Rinsho to Yakubutsu Chiryō*, 14(4):304, 1995).
 [0004] For example, in urinary dysfunction associated with prostatic hyperplasia, the urinary dysfunction is generated by both urethral stricture (mechanical obstruction) caused by compression of enlarged prostate and over-shrinkage (functional obstruction) of smooth muscle of prostate accompanied by an increase in $\alpha 1$ receptors in the enlarged prostate (cf. *Rinsho Kagaku*, 33(12):1542, 1997).
- 25 [0005] On the other hand, neurogenic bladder is a general term for abnormal urination caused by disorder of sympathetic nerve, parasympathetic nerve, etc. controlling the action of bladder and urethra but it does not stand for localizing and systematic diseases (cf. "Hyojun Hinyōki Kagaku", the fifth edition, published in 1998).
 [0006] Main diseases which cause neurogenic bladder are (1) encephalopathy such as dementia, cerebrovascular disturbance, cerebral wound, encephalitis, brain tumor, multiple sclerosis, Parkinson disease, Shy-Grager syndrome and olivopontocerebellar atrophy; (2) spondylopathy such as spinal cord injury, spinal cord tumor, spondylitis, myelopathy, vascular disease of spinal cord, spinal cord diseases (such as cervical spondylosis, disk herniation and cervical ossification of posterior longitudinal ligament), spina bifida and multiple sclerosis and (3) peripheral nerve disturbance such as diabetes mellitus, operations in pelvic cavity (for radical therapy of uterine cancer and rectum cancer), spinal cord diseases (such as disk herniation, spinal cord stenosis, lumbar separation and spondylolisthesis), Guillan-Barre
- 30 syndrome, pelvic fracture and cauda equina nerve tumor.
 [0007] In the urinary dysfunction associated with neurogenic bladder, there are a voiding dysfunction and a strage dysfunction and each of those dysfunction may take place either independently or jointly depending upon phase, site, etc. of the dysfunction. In the voiding dysfunction, symptoms such as retardation of initiation of urination, prolongation of time for urination intermittent urination, minute urinary stream, etc. appear.
- 40 [0008] At present, the drugs where the effectiveness in clinic has been confirmed as a therapeutic agent for voiding dysfunction associated with neurogenic bladder in Japan, Europe and U. S. A. are cholinergic drugs only and their effect is to improve the urinary disturbance by recovering the shrinking force of bladder of a low active type where detrusor reflex is lost.
 [0009] Since there is no animal model for reflecting the symptom in neurogenic bladder, development of the therapeutic drugs therefor is difficult and even if a few effective cases were clinically confirmed in some substances other than the above-mentioned cholinergic drugs, no drug which can be competent for practical use as the drug has been obtained yet.
- 50 [0010] Investigation has been carried out for a possibility for the therapy of neurogenic bladder based upon an improvement of urinary efficiency by a decrease in urethral resistance by administration of an α -receptor antagonists such as phenoxybenzamine and prazosin hydrochloride to adrenergic sympathetic nerve which is abundantly distributed in smooth muscle of neck of urinary bladder and urethra of prostate. However, there has been almost no success as a drug which can be competent in clinic.
 [0011] There has been a demand for developing a therapeutic drug having a new action mechanism which can be competent in practical use as a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

55

Disclosure of the Invention

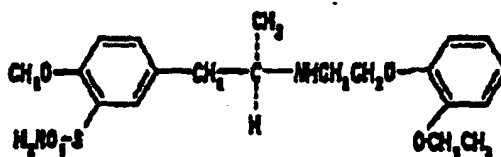
- [0012] Under such circumstances, the present inventors have found that tamsulosin or a salt thereof is effective for

the therapy of voiding dysfunction of the patients with neurogenic bladder.

[0013] Thus, the present invention relates to a pharmaceutical composition for the therapy of voiding dysfunction associated with neurogenic bladder where the composition contains tamsulosin or a pharmaceutically acceptable salt thereof as an effective component.

5 [0014] The present invention further relates to the use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for voiding dysfunction associated with neurogenic bladder. The present invention furthermore relates to a method for the therapy of voiding dysfunction associated with neurogenic bladder where the method includes administration of a therapeutically effective dose of tamsulosin or a pharmaceutically acceptable salt thereof to a patient.

10 [0015] The chemical name for tamsulosin is (R)-(-)-5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide which is represented by the following structural formula. Tamsulosin has been firstly disclosed in the Japanese Laid-Open Patent Publication No.56-110665 together with its pharmaceutically acceptable salts.



[0016] Tamsulosin or a salt thereof has been known to have a blocking action to adrenaline α_{1A} receptor and particularly its hydrochloride (tamsulosin hydrochloride) has been known to have a blocking action to α_1 receptor in urethra and prostate and to reduce the prostatic pressure in the urethral inner pressure curve whereby the urinary dysfunction associated with benign prostatic hyperplasia is improved.

[0017] However, there has been no report for confirming the effectiveness to voiding dysfunction associated with neurogenic bladder wherein the onset mechanism is different. Now the present inventors have clinically confirmed for the first time that tamsulosin hydrochloride is effective for the therapy of voiding dysfunction associated with neurogenic bladder.

[0018] Incidentally, although there have been several reports for the clinical applications to neurogenic bladder by other α -receptor antagonists such as prazosin hydrochloride, bunazosin hydrochloride, moxislyte and urapidil, there has been no α -receptor antagonist which can be confirmed to be clinically effective as a therapeutic agent for voiding dysfunction associated with neurogenic bladder in Japan, Europe and U. S. A. For example, with regard to bunazosin hydrochloride, an application for additional use for voiding dysfunction associated with neurogenic bladder was filed with the Ministry of Health and Welfare in Japan but no permission was obtained whereby such an attempt has been given up (cf. *Asu no Shinyaku*, 1998/Pharma Projects).

[0019] The present invention will be further illustrated as hereunder.

[0020] Tamsulosin and pharmaceutically acceptable salts thereof are easily available either by the methods mentioned in the Japanese Laid-Open Patent Publications No.56-110665 and 62-114952 or by the methods similar thereto.

[0021] Tamsulosin is able to form pharmaceutically acceptable acid- and base-addition salts with a large extent of inorganic and organic acids and bases. Such salts constitute a part of the present invention as well. Their examples are salts with inorganic acid such as hydrochloric acid, sulfuric acid and phosphoric acid; salts with organic acid such as fumaric acid, malic acid, citric acid and succinic acid; salts with alkali metal such as sodium and potassium; and salts with alkali earth metal such as calcium and magnesium. The most preferred salt in the present invention is a hydrochloride.

[0022] The pharmaceutical agents of the present invention can be prepared as solid preparations for oral use, liquid preparations for oral use or injection preparations by conventional methods using organic or inorganic carriers, vehicles or other additives which are suitable for oral or parenteral administration. Preferred forms are solid preparations for oral use which are able to be taken by the patients themselves and also are convenient for storing and carrying and, to be more specific, they are tablets, diluted powder, granules, fine particles, capsules, pills, etc.

[0023] In such solid preparations, the active substance is mixed with at least one inert diluent such as lactose, mannitol, glucose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc. The composition may contain additives other than the inert diluent by conventional methods such as a binder (e.g., hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc.), a lubricant (e.g., magnesium stearate, calcium stearate, polyethylene glycol, starch, talc, etc.), a disintegrating agent (e.g., cellulose calcium glycolate), a stabilizer (e.g., lactose), a solubilizing aid (e.g., glutamic acid, aspartic acid, etc.), a plasticizer (e.g., Tween 80, triacetin, etc.) and a coloring agent (e.g., titanium oxide and iron sesquioxide). If necessary, tablets or pills may be coated with a sugar coat or

film soluble in stomach or in intestine such as sucrose, gelatin, agar, pectin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate, etc.

[0024] The most preferred form in the present invention is a sustained release preparations of a prolonged release type. Sustained release preparations may be made into tablets, granules, fine particles or capsules by conventional methods. Sustained release preparations are prepared by coating tablets, granules, fine particles or capsules with, for example, fat/oil, polyglycerol fatty acid ester, hydroxypropyl cellulose, etc. by conventional methods.

[0025] The sustained release preparation which is disclosed in the Japanese Laid-Open Patent Publication No.62-000009 is particularly preferred. Thus, each unit preparation is prepared in such a manner that a dissolution suppressor is added to a mixture of an active compound and 50% by weight or more of a unit-forming substance in the unit followed by granulating and the resulting particles are filled in a capsule to prepare a capsule preparation or are made into tablets by conventional methods. Crystalline cellulose is preferred as a unit-forming substance. With regard to the dissolution suppressor, water-insoluble high-molecular substance such as acrylate polymer or copolymer or cellulose derivative are used and it is preferred that such a substance is used in a form of an aqueous suspension, an aqueous emulsion or a solution in a water-containing organic solvent. Examples of the commercially available ones are Eudragit L30D-55 (methacrylate copolymer LD), Eudragit E30D (emulsion of copolymer of ethyl acrylate with methyl methacrylate) and Aqua Coat ECD-30 (aqueous suspension of ethyl cellulose) and they are used as dissolution suppressors as they are or after diluting with water if necessary.

[0026] The dose of tamsulosin or a pharmaceutically acceptable salt thereof may be appropriately decided for each individual by taking administration route, symptom of the disease, age of the patient to be administered, sex, etc. into consideration. In the case of oral administration of tamsulosin hydrochloride, the usual dose in terms of the effective component for adult is usually about 0.1 to 0.8 mg/day or, most preferably, 0.2 to 0.4 mg/day and this is orally administered once daily after a meal.

[0027] Although the pharmaceutical agent of the present invention is well effective by a single administration, it is also possible that said agent is used together with a cholinergic drug such as distigmine bromide, bethanechol chloride, etc. or with other central nervous system drugs either simultaneously or with time interval. It is further possible that said agent is used together with a therapeutic agent for causal diseases for neurogenic bladder.

Industrial Applicability

[0028] In accordance with the present invention, an excellent therapeutic agent for voiding dysfunction associated with neurogenic bladder where said agent is able to be competent for actual use in clinical field can be offered.

Best Mode for Carrying Out the Invention

[0029] The present invention will now be further illustrated by way of the following examples and test examples although the present invention is not limited to those examples, etc.

Example 1.

[0030] Tamsulosin hydrochloride (5 g) and 470 g of crystalline cellulose were well mixed and a mixture of 83.3 g of Eudragit L30D-55 (25 g as a solid) with water to make 500 g was added thereto followed by granulating using a high-speed stirring granulating machine. The resulting particles were spherical having a particle size of 0.1-1.5 mm where most of them were in 0.2-1.0 mm.

[0031] The resulting particles were mixed with talc and magnesium stearate and the mixture was filled in capsules to prepare the capsule preparation. (Each capsule contained 0.2 mg of tamsulosin hydrochloride.)

Examples 2-6.

[0032] The particles which were manufactured by the same manner as in Example 1 according to the formulations of Table 1 were made into the capsule preparations.

Table 1

(unit: grams)			
Example Number	Tamsulosin Hydrochloride (g)	Crystalline Cellulose (g)	Eudragit L30D-55 (Solid Content) (g)
2	5	445	166.6 (60)
3	5	395	333.3 (100)
4	5	482.5	41.7 (12.5)
5	2.5	472.5	83.3 (25)
6	1.25	473.75	83.3 (25)

Example 7.

[0033] Tamsulosin hydrochloride (5 g), 420 g of crystalline cellulose and 50 g of magnesium stearate were well mixed and a mixture of 83.3 g of Eudragit L30-D-55 (25 g as a solid) with water to make 500 g was added thereto followed by kneading and granulating using a centrifugal fluidized granulating machine. The resulting particles were spherical having a particle size of 0.1-1.5 mm where most of them were in 0.2-1.0 mm.

[0034] The resulting particles were mixed with talc and magnesium stearate and the mixture was filled in capsules to prepare the capsule preparation. (Each capsule contained 0.2 mg of tamsulosin hydrochloride.)

Examples 8-10.

[0035] The particles which were manufactured by the same manner as in Example 7 according to the formulations of Table 2 were made into the capsule preparations.

Table 2

(unit: grams)				
Example Number	Tamsulosin Hydrochloride	Crystalline Cellulose	Magnesium Stearate	Eudragit L30D-55 (Solid Content)
8	5	460	10	83.3 (25)
9	5	445	25	83.3 (25)
10	2.5	462.5	10	83.3 (25)

Example 11.

[0036] Hydrogenated castor oil (80 g) was melted, 10 g of tamsulosin hydrochloride and 30 g of lowly-substituted hydroxypropyl cellulose were dispersed therein and the mixture was made into fine particles by means of a spray congealing. The resulting fine particles (60 g) and 440 g of crystalline cellulose were well mixed, 500 g of water were added thereto and the mixture was granulated by a centrifugal fluidized granulating machine.

[0037] The resulting particles were mixed with talc and magnesium stearate followed by filling in a capsule to prepare a capsule preparation.

[0038] Test Example 1. Clinical Test to Patients of Voiding Dysfunction Associated with Neurogenic Bladder.

[0039] Clinical test was carried out under the following conditions to the cases of voiding dysfunction associated with neurogenic bladder.

[0040] Patients: Sixty patients diagnosed to be voiding dysfunction associated with neurogenic bladder (excluding the cases where the cause was peripheral diseases).

[0041] Used drug and method of administration: Capsule preparation containing 0.2 mg of tamsulosin hydrochloride or placebo capsule was used and two capsules were orally administered after breakfast (once daily) for four weeks.

[0042] Test period: (1) Wash-out stage: When any therapeutic drug to the disease was given previously, a wash-out

period for seven days or longer before starting the observing stage was provided; (2): Observing stage: The observing stage was three days or longer and, when stabilization of the subjective symptoms were confirmed, the therapeutic stage was started; (3): Therapeutic stage: The therapeutic stage was four weeks (28 days).

[0043] Observing Items and Terms:

5

10

15

20

25

Test Items	Wash-Out Stage	Observing Stage	Therapeutic Stage		
	≥ 7 Days -10 Days	≥ 3 Days -3 Days	0 Day	2 Weeks	4 Weeks (Completion)
Measuring Intracystic Pressure	●	●			
Subjective Symptoms*)		●	●	●	●
Impression by Patients			●	●	●
Measuring Urinary Flow + Residual Urine		●	●	●	●
Blood Pressure + Heart Rate		●			●
Clinical Test		●			●
Side Effect / Accidental Symptom		●	●	●	●

*) Subjective Symptoms: (1) Frequency of urination at daytime;
 (2) Frequency of urination at night; (3) Self-catheterization;
 (4) Retardation in initiation of urination; (5) elongation of
 urination time; (6) Strain upon urination; (7) Stoppage of
 urinary stream; (8) Vigor or dash of urination; (9) Frequency
 of urinary incontinence.

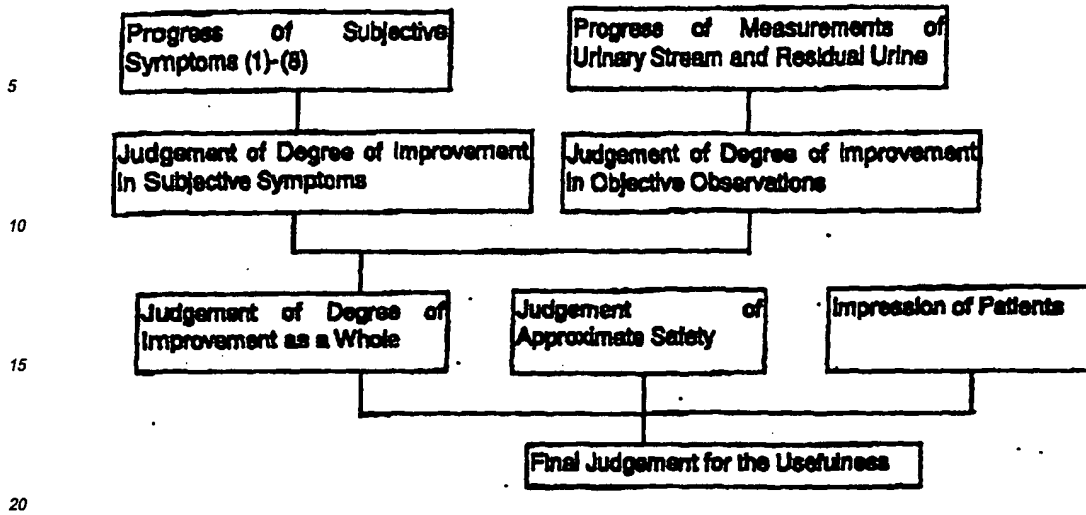
40

[0044] Method of Evaluation: Evaluation was done according to the following flow chart.

45

50

55



[0045] Result: Table 3 shows the progress of the subjective symptoms (1)-(8) in terms of changing rate (decreasing rate) of the total score and the progress of the urinary flow and residual urine in terms of changing amounts of maximum flow stream rate, average urinary flow rate and residual urine rate.

Table 3

	Tamsulosin Hydrochloride-Administered Group	Placebo-Administered Group
Total Score (Changing Rate)	-31±34.2% (n=23)	-29±31.9% (n=22)
Maximum Urinary Flow (Changing Amt)	2.5±3.01ml/sec (n=16)	-0.6±7.52ml/sec (n=15)
Average Urinary Flow (Changing Amt)	1.2±1.86ml/sec (n=16)	-0.2±4.26ml/sec (n=15)
Residual Urine Amount (Changing Amt)	-18±80.1ml (n=23)	-55±128.9ml (n=15)
Residual Urine Rate (Changing Amt)	-13±20.0% (n=16)	-4±24.1% (n=15)

[0046] Degrees of improvement in subjective symptoms and objective observation and degree of improvement as a whole were evaluated as significant improvement, medium improvement, light improvement, unchanged and worsening depending upon the above-mentioned result.

[0047] Approximate safety was evaluated as no problem, little problems, some problems and problems according to the presence/absence and degree of side effect, change of blood pressure and pulse rate, and abnormal change in clinical data.

[0048] Impression by the patient was judged to be much improvement, improvement, some improvement, no change, some worsening, worsening and much worsening.

[0049] Finally, degree of improvement as a whole, approximate safety and impression by patient were taken into consideration and the final judgement for the Usefulness was judged to be any of the five groups - very useful, useful, somewhat useful and not preferable.

[0050] With regard to the approximate safety and impression by patient, there was no significant difference between the groups administered with tamsulosin hydrochloride and with placebo.

[0051] The result is shown in Table 4.

Table 4

		Tamsulosin Hydrochloride-Administered Group	Placebo-Administered Group
Degree of Improvement in Subjective Symptoms	≥Medium Improvement	43.5% (10/23)	31.8% (7/22)
Degree of Improvement in Objective Observation	≥Medium Improvement	60.0% (12/20)	23.5% (4/17)
Degree of Improvement as a Whole	≥Medium Improvement	60.0% (12/20)	23.5% (4/17)
Usefulness	≥Useful	52.2% (12/23)	17.6% (3/17)

[0052] Tamsulosin hydrochloride showed significant improvement in the improvement of subjective symptom and objective observation of the patients suffering from voiding dysfunction associated with neurogenic bladder and also in the improvement as a whole. When the impression by the patients was further taken into consideration, it was confirmed that tamsulosin hydrochloride was useful as a therapeutic agent for voiding dysfunction associated with neurogenic bladder.

Claims

1. A pharmaceutical composition for the therapy of voiding dysfunction associated with neurogenic bladder where said composition contains tamsulosin or a pharmaceutically acceptable salt thereof.
2. A pharmaceutical composition for the therapy of voiding dysfunction associated with neurogenic bladder according to claim 1 in which said composition contains tamsulosin hydrochloride.
3. The use of tamsulosin or a pharmaceutically acceptable salt thereof for the manufacture of a therapeutic agent for voiding dysfunction associated with neurogenic bladder.
4. A method for the therapy of voiding dysfunction associated with neurogenic bladder where said method includes administration of tamsulosin or a pharmaceutically acceptable salt thereof to a patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/03343

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl. ⁶ A61K31/18 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl. ⁶ A61K31/18 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CA (STN), MEDLINE (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF UROLOGY, Vol. 156, No. 3, p.1125-1130, 1996 "The effect of urapidil on neurogenic bladder : a placebo controlled double-blind study" Yasuda K et al.	1-3
A	NEUROUROLOGY AND URODYNAMICS, Vol. 15, No. 2, p.119-131, 1996 "Effect of intravenous alfuzosin on urethral pressure in patients with neurogenic bladder dysfunction" Perrigot M et al.	1-3
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 20 September, 1999 (20. 09. 99)		Date of mailing of the international search report 28 September, 1999 (28. 09. 99)
Name and mailing address of the ISA/ Japanese Patent Office		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/03343

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4
because they relate to subject matter not required to be searched by this Authority, namely:
It pertains to methods for treatment of the human body by therapy (under the provisions of Rule 39.1 (iv) of the Regulations under the PCT).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.